

Cochrane Scientific
Committee
AGENDA

5th June 2018

Teleconference



DT – David Tovey, Editor in Chief, JC – Jackie Chandler, Methods Co-ordinator

Committee members:

Corinna Dressler (CD)

Research Associate at the Division of Evidence-Based Medicine (dEBM) at the Charité – Universitätsmedizin Berlin, Germany

Donna Gilles (DG)

Senior Researcher, Clinical Performance Mental Health Network, Western Sydney, Australia and editor for both the Cochrane Developmental, Psychosocial and Learning Problems Group and Diagnostic Test Accuracy Review Group.

Julian Higgins (JH)

Professor of Evidence Synthesis at the School of Social and Community Medicine, at the University of Bristol, Bristol, UK, and current Senior Scientific Editor of the *Cochrane Handbook of Systematic Reviews for Interventions*.

Asbjørn Hróbjartsson (AH)

Professor of Evidence-Based Medicine and Clinical Research Methodology at the University of Southern Denmark, and Head of Research for the Center for Evidence-Based Medicine at Odense University Hospital, which hosts the secretariat of the Cochrane Bias Methods Group.

Ana Marusic (AM)

Professor of Anatomy and Chair of the Department of Research in Biomedicine and Health at the University of Split School of Medicine, Split, Croatia and founder of Cochrane Croatia.

Jane Noyes (JN)

Professor of Health and Social Services Research and Child Health, Bangor University, Wales, UK, lead Convenor of the Cochrane Qualitative and Implementation Methods Group, and a UK Cochrane Fellow.

Tomas Pantoja (TP)

Associate Professor, Family Medicine Department, School of Medicine, Pontificia Universidad Católica de Chile and Editor of the Cochrane Effective Practice and Organisation of Care (EPOC) Group.

Philippe Ravaud (PR)

Professor of Epidemiology, Faculty of Medicine, Head of the Clinical Epidemiology Centre, Hôtel-Dieu Hospital, Paris Descartes University, France and Director of Cochrane France.

Johannes Reistma (JR)

Associate Professor at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands and a member of both the

Cochrane Diagnostic Test Accuracy Working Group and the Screening and Diagnostic Tests Methods Group.

Rebecca Ryan (RR)

Research Fellow at the School of Psychology and Public Health, La Trobe University, Australia and Deputy Co-ordinating Editor of the Cochrane Consumers and Communication Group.

Christopher Schmid (CS)

Professor of Biostatistics, founding member and Co-Director of the Center for Evidence Synthesis in Health, Brown School of Public Health, US, Fellow of the American Statistical Association (ASA) and Founding Co-Editor of *Research Synthesis Methods*.

Nicole Skoetz (NS)

Scientific Co-ordinator, Working Group Standard Operating Procedures of the Comprehensive Cancer Centers, Center of Integrative Oncology Köln Bonn, and Co-ordinating Editor Cochrane Haematological Malignancies Group, Department of Internal Medicine, University Hospital of Cologne.

Nichole Taske (NT)

Associate Director (Methodology), Centre for Guidelines, NICE, U

AGENDA ITEM	Details and links to documents	Responsibility for item
1) Welcome and apologies received	Apologies received from Hans Reitsma	Chairs & JC
2) Approval of previous minutes	Minutes dated 28 th February (Paper 1)	Chairs
a) Matters arising	<p>5. (2) Expert panel report on whether using sequential methods to adjust P values is necessary in repeated meta-analyses. CS will update the meeting on progress with the expert panel report and the plan for a short position statement that qualifies the nature of the recommendation made, and under what circumstances review authors might use these methods e.g. exploratory analyses.</p> <p>8. Any other business JH raised an item regarding scientific misconduct and whether there was an expectation to actively search for any errors or misconduct in study reports rather than respond to items that come to light. JH to circulate draft section to AM and DT.</p>	Chairs & JC
3) CSC Business matters	None	DT & JC
4) Submissions	No further submissions	CSC members
5) Methods for CSC Review	<p>Data-based predictive distributions for between-study heterogeneity</p> <p>In small meta-analyses, a conventional random-effects meta-analysis is problematic because between-study heterogeneity is imprecisely estimated, and this imprecision is not taken into account. A Bayesian meta-analysis allows researchers to incorporate external evidence on the likely extent of between-study heterogeneity in their particular research setting. Rebecca Turner will attend and present at the meeting. (Paper 2)</p>	CSC members

6) Methods for CSC sign off and recommendation	None	CSC members
7) Special items		
a) Research priorities and strategy	None	CSC members
8) Any Other Business		
9) Meeting schedule	List of meetings 16 th September 2018 at 7.30am (Colloquium) informal and invite the Methods Executive (overlapping membership). 8 th November 2018 at 11.00am UK GMT	JC

Cochrane Scientific Committee

Teleconference 28th February 2018

Notes and abbreviations

Members of the CSC present

Corinna Dressler (CD)	Present
Donna Gilles (DG)	Present
Julian Higgins (JH)	Present
Asbjørn Hróbjartsson (AH)	Present
Ana Marusic (AM)	Present
Jane Noyes (JN)	Present
Tomas Pantoja (TP)	Present
Philippe Ravaud (PR)	Present
Johannes Reistma (JR)	Present
Rebecca Ryan (RR)	Present
Christopher Schmid (CS)	Present
Nicole Skoetz (NS)	Present
Nichole Taske (NT)	Apologies
David Tovey (DT)	Present

Other attendees

Jackie Chandler	Minutes
Peter Doshi	Invited speaker
Tom Jefferson	Invited speaker

AGENDA ITEM	Minutes
1) Welcome and apologies received	
2) Approval of previous minutes	Minutes dated 18 th October 2017
a) Matters arising	List of items
	3. CSC Business matters – Clarifying role of CSC to the wider Cochrane Community
	ACTION: Discussed possible urgent items that might arise from the revisions to the Handbook – none arose so no intermediate action required.
	ACTION: A table of contents for V6 of the Handbook as requested by members was produced.
	ACTION: No items received from members for the attention of the committee or the Handbook Editors. Handbook Editors did not identify any methods warranting CSC sign off at this point.
	5. Methods for CSC Review - Follow up comments for ROBINS I

ACTION: No further update on the development of a competency statement to use ROBINS I. However, competency for complex methods, a wider issue, is under consideration.

7. Special items:

a. Research priorities and strategy

ACTION: Following on from the view that the CSC could not reasonably co-ordinate its own agenda, processes to filter items to the Committee was on the agenda and is reported below.

3) CSC Business matters

Placing the Scientific Committee in Cochrane's new structures.

DT addressed a slide that set out key decision-making structures on methods: Governing Board (GB), Editorial Board (EB), Scientific Committee (SC) and the Methods Executive (ME). GB previously involved in operational activities now assumes a strategic role in providing organisational governance. DT also referred to the role of the Council as a Cochrane community representative body with an advisory role to the GB. The EB provides strategy for the Library setting success criteria to deliver ongoing improvements. EB comprises the Network senior editors and several specialist advisers for methods, knowledge translation and end users. SC decides what methods are appropriate for use in Cochrane, and the EB on how these methods are implemented. The role of the ME as the representative body for the Methods Community actively brings forward methods for consideration at SC level and will make decisions on uncontested improvements or developments. DG proposed an amendment to the SC definition in the slide "Evaluates both new and contested methods for recommendation and endorsement on their *scientific* robustness for implementation". Revision attached.

4) Submissions

We now manage an open call portal for agenda items, although no further submissions received. The process for getting items on the agenda for CSC evaluation now benefits from a recent organisational review. A supporting structure for methodologists, the Methods Executive, will take on the role of filtering methods for implementation and escalate, when appropriate, to the Scientific Committee. This body will also filter proposals from the Methods Groups, other methodologists and any submissions received via the online portal.

5) Methods for CSC Review

1. Interim guidance on how to decide whether to include clinical study reports and other regulatory documents into Cochrane Reviews. Please see CSC report statement appended.

Attachments A and B.

Following a presentation from Peter Doshi and Tom Jefferson a detailed discussion followed in which CSC members acknowledged the important problem of reporting bias and that further investment to develop the necessary tools and methods was warranted if we want to include these types of documents in Cochrane Reviews. For Cochrane to invest requires balancing several challenges as set out in the Content Development Strategy (CDS). The CSC considered use of these documents scientifically important given the principle that

they provided the most complete data from any individual study. Development of better methods for incorporating such documents into reviews will follow when those with expertise and resources use them in reviews. DT reported that currently stakeholders were not demanding this type of information to inform reviews. Proposals for further development would be considered within the CDS. Members also believed such fundamental infra-structure changes resulting from widespread roll out of this type of data acquisition and assessment warranted discussions with both the EB and GB.

2. Expert panel report on whether using sequential methods to adjust P values is necessary in repeated meta-analyses.

This is an interim report based on two panel meetings, panel members would like further time to finesse the final report. Please see CSC report statement appended.

Attachment C

After discussion following CS's report back from the panel. The CSC agreed that these methods could not be recommended and that the expert panel in finalising their report and recommendation are asked to qualify their recommendation to specify that the CSC recommends sequential methods are not used for general use in Cochrane and are only justifiable in particular cases.

ACTION: CS to review and update report

6) Methods for CSC sign off and recommendation	None
7) Special items	
a) Research priorities and strategy	The development of a Cochrane Content Strategy, led by David Tovey, will create processes and structures that include surveillance and monitoring systems for content developments, and regular stakeholder audits to ascertain their evidence needs. Content refers to addressing different types of questions, using multiple types of data, new methods and how these complement end users and those that make health care decisions. New areas of content will also involve technological advancements, such as automation. The Cochrane Scientific Committee along with other bodies in Cochrane plays a key role in supporting this strategy.
8) Any Other Business	JH raised an item regarding scientific misconduct and whether there was an expectation to actively search for any errors or misconduct in study reports rather than respond to items that come to light. Reference was made to MECIR C48. CSC members considered this reflected expected practice. Handbook Editors are updating the Collecting data chapter in the Handbook and wanted to ensure they were in line with current policy and ensure errors or misconduct are recorded in the bias tool when suspicions are raised when extracting data. This is a complex area in identifying as to whether an error or misconduct has occurred, e.g. previous author retraction not relevant to current study. JH to get draft reviewed by AM and DT and

other EMD staff. There is an expectation that authors are vigilant and ensure errors or misconduct are identified.

ACTION: JH to circulate draft section to AM and DT.

9) Meeting schedule

List of meetings:

5th June 2018 @ 12pm BST.

The proposed face to face meeting in Edinburgh is postponed till next year at the midyear governance meeting.

October/November meeting dates circulating.

Cochrane Scientific Committee

Recommendation statement/report

Date: 28th February 2018

Relates to agenda item and meeting reference: 5.1

Priority: Medium

Open access/restricted: Open

INTERIM GUIDANCE ON HOW TO DECIDE WHETHER TO INCLUDE CLINICAL STUDY REPORTS AND OTHER REGULATORY DOCUMENTS INTO COCHRANE REVIEWS

Lead developers/investigators: Tom Jefferson, Peter Doshi, Lesley Stewart, Isabelle Boutron, Carol Lefebvre, Mark Jones, Su Golder and Alex Hodkinson

Abstract:

Aim & objective: To produce interim guidance on the circumstances under which clinical study reports and other regulatory documents should be considered for inclusion in Cochrane Reviews, either in addition to or instead of data from more traditional sources.

Methods for development: There is very little evidence on which to develop guidance and identify a rule for determining which reviews would most benefit from the inclusion of such data. Experts used their own experience and knowledge having surveyed the literature. They also undertook a survey of both Cochrane and non-Cochrane authors to ascertain current practice. The guidance focuses on clinical study reports and other regulatory documents relating to pharmaceuticals and biologics for which these documents generally exist. Authors admit, however, that non-pharmaceutical interventions (such as implantable devices, surgery, rehabilitation, behavioural interventions and diagnostics) are responsible for a large part of healthcare expenditure and that regulatory activity and transparency have been recently increasing in this area, at a slower pace, however, particularly the field of devices.

Results/Development: Table 1 (pp 8-11) in the guidance contains a selected and illustrative list of studies that have compared different sources of data for the same trial, such as publication vs. CSR or trial register entries vs. publications. Although this is not an exhaustive list of all such studies, it covers more than 50 different interventions and offers glimpses of the ways in which reporting bias affects the biomedical literature. Survey results on current review author practice from 160 respondents found 20/160 (13%) of the respondents had previously requested or used CSRs and other regulatory documents, 7/160 (4%) had considered it, and 133/160 (83%) had never considered it. Data sought by survey respondents were mainly from the EMA and/or the FDA (19 (40%) of the 47 requests made by those previously requesting CSRs in total) and/or directly from pharmaceutical companies (18/47 (38%)). 5/47 (11%) of the requests included non-regulatory data requests to authors of published trials. Amongst the 20 respondents that requested regulatory data, 12 (60%) involved CSRs, five obtained medical and statistical reviews

from the FDA and two European public assessment reports (EPARs). The main reasons for accessing CSRs were concerns about reporting biases 11/20 (55%), outcome reporting bias and publication bias (5/20 - 25%). Trigger criteria were developed (Table 3, p14) and tested on a survey of n=21 survey responders who had used such data, results are provided on level of importance in Figure 1, p15.

Final product: A report provides interim guidance on how to decide whether to include clinical study reports and other regulatory documents in to Cochrane Reviews, and includes a glossary of document types with definition and document image. This guidance does not address how to access, assess and extract regulatory data. Report authors conclude that Cochrane should consider making regulatory data a preferred source, primarily when the intervention in question is of potential high value and when there is evidence of reporting bias, or both. Cochrane should invest in its infrastructure to make this possible.

SUPPORTING DOCUMENTATION

Presentation: [link](#)

Editorial (received post meeting): Redefining the 'E' in EBM. Jefferson T, Jørgensen L. BMJ Evidence-Based Medicine. Epub ahead of print: 9 March 2018. doi:10.1136/bmjebm-2018-110918

CSC RECOMMENDATION

Highly recommended

Because

Recommended with provisions

Because

Optional/advisory (one among several options)

CSC members agreed this data was important in tackling reporting bias. Further development of methods and tools were required that identifies where more evidence is needed as well as where Cochrane should concentrate its energies. The report's findings were accepted in principle by the committee. However, further consideration of roll out and implementation within the main body of Cochrane required the input of both Governing Board (resources) and Editorial Board (implementation requirements).

Not recommended

Because

CSC STATEMENT

Summary statement

Following a presentation from Tom Jefferson and Peter Doshi (providing disclosures) raising their concerns on reporting bias in Cochrane Reviews they asked, as a matter of urgency, Cochrane starts to debate how and when it should expect Cochrane Reviews to look beyond published journal reports where other unpublished data is available for scrutiny. Tom provided a specific definition for the types of reviews this report covered:

Anything which is generated in the course of submission for a marketing organisation for a drug or biologic or a particularly invasive device. Excluded from this anything not going to market and interventions for which we have no clinical data, so no full reports.

Identification of the different types of documents and the basis on which the information is collated was a key objective to developing the glossary: CSRs were complete reports of trials, whereas medical officer reports were an individual's own report of peer review comments on the trial's original report. It was noted that all these documents were equally prone to error but they provided more complete information than published reports. Also, they are not always easy to read. The glossary tries to aid the navigation of these documents. They provide multiple sources of information to cross check data whereas typically Cochrane Reviews rely upon a single report that is not able to provide all the data and information collected during the trial. The Restoring Invisible and Abandoned Trials (RIAT) Support Center will support the interactive glossary.

CSC members agreed the problem existed and discussed primarily the best approach that Cochrane, given its resources, could take. The following key points were made:

- The Cochrane community needed to discuss its approach and support for using this type of data before mobilising funds and resources.
- The field is in its infancy.
- To move methods forward greater familiarity with these documents was required.
- Experimental or exemplar reviews needed to be undertaken to test Cochrane processes and infra-structure.
- Although, not on most people's radar and with confusion over terms used it was noted as a matter of principle Cochrane should use the most truthful report of the trial. An example of the discrepancy was that the compression of the original report into a journal article was in a ratio of 8000 pages to 1.
- Availability of data will vary by drug and regulator. Although some regulators e.g. EMA are now providing this data freely.
- Issues for authors are time to obtain these documents, risk of inexperience causing errors in synthesis by the reviewer, complex methods required.
- Need to clarify when it is sensible to undertake review of this data and the identify the resources to ensure it is conducted properly.
- Not required for every title, therefore we need prioritisation of which titles to support.
- Collaboration between Cochrane and regulatory bodies could be fruitful.
- Undertaking such high-profile reviews important reviews using these documents may impact on the number of overall reviews undertaken in Cochrane.

Credibility & validity: The issue of reporting bias with journal publications is well established.

Limitations/caveats: All data collated has limitations and scrutiny of the data requires authors able to identify any problems when reviewing these documents.

Areas of concern/uncertainty: Primarily development of methods and tools to aid authors.

Impact on Cochrane: Further internal discussions are required.

Cochrane resources needed: Feasibility and assessment of infra-structure developments is required before full scale roll out.

Cochrane Scientific Committee

Briefing report – Methods review

Date: 5th June 2018

CSC: 2:18

Agenda item: 5 Rebecca Turner will attend to present her paper to the committee

Priority: Low/medium

Open access/restricted: Open

DATA-BASED PREDICTIVE DISTRIBUTIONS FOR BETWEEN-STUDY HETEROGENITY

Lead developers/investigators: Rebecca Turner, Jonathan Davey, Mike Clarke, Simon Thompson and Julian Higgins (conflict previously declared)

Abstract:

Many meta-analyses contain only a small number of studies: in a descriptive analysis of the Cochrane database, Davey 2011¹ found that 75% of meta-analyses reported in Cochrane Reviews included five or fewer studies. In small meta-analyses, a conventional random-effects meta-analysis is problematic because between-study heterogeneity is imprecisely estimated, and this imprecision is not taken into account.

A Bayesian meta-analysis allows researchers to incorporate external evidence on the likely extent of between-study heterogeneity in their particular research setting.

Aim & objective

To assist with implementation of Bayesian meta-analysis, this project set out to provide empirical evidence on how much between-study heterogeneity could be expected in various healthcare settings.

Methods for development

Meta-analyses from the Cochrane Database of Systematic Reviews (Issue 1, 2008) were classified according to the type of outcome, type of intervention comparison and medical specialty. The impact of meta-analysis characteristics on the underlying between-study heterogeneity variance was investigated by modelling the study data from all meta-analyses simultaneously. Meta-analyses of binary outcomes and meta-analyses of continuous outcomes were modelled separately.

Predictive distributions were obtained for the between-study heterogeneity expected in future meta-analyses. These distributions can be used directly as data-based informative prior distributions for heterogeneity in Bayesian meta-analyses.

Results/Development

Between-study heterogeneity was found to be strongly associated with the type of outcome measured in the meta-analysis and somewhat associated with the types of interventions compared. For example, between-study heterogeneity variances for meta-analyses in which the outcome was all-cause mortality were found to be on average 17% (95% CI 10% to 26%) of variances for other outcomes. In meta-analyses comparing two active pharmacological interventions, heterogeneity was on average 75% (95% CI 58% to 95%) of variances for non-pharmacological interventions.

We have published predictive distributions for heterogeneity for various different settings, defined by type of outcome and type of intervention comparison, separately for meta-analyses of binary outcomes^{2,3} and for meta-analyses of continuous outcomes⁴. In addition, we have proposed accessible methods for implementing Bayesian meta-analysis with informative priors, avoiding the need for specialist Bayesian software^{3,5}.

Conclusion

Using informative priors for heterogeneity in a Bayesian meta-analysis would be beneficial in meta-analyses including few studies. We have provided resources to facilitate this approach. These methods could be applied within Cochrane Reviews.

Final product: Guidance currently available in journal articles.

Impact: Provides an additional technique that improves the analysis of reviews with few studies, which is a large proportion of Cochrane Reviews.

Resources needed: Training and guidance aimed at statisticians and editors – Question about

Recommendation requested: To consider whether the adoption of this analytic technique should be adopted routinely or selectively in Cochrane Reviews.

SUPPORTING DOCUMENTATION

Attached to this document is the primary paper Turner and colleagues “Predicting the extent of heterogeneity in meta-analysis, using empirical data from the *Cochrane Database of Systematic Reviews*” *International Journal of Epidemiology*. 2012;41:818-827.

Additional supportive information is available in the Scientific Committee Dropbox June meeting folder:

1. Davey J, Turner RM, Clarke MJ, Higgins JPT. Characteristics of meta-analyses and their component studies in the Cochrane Database of Systematic Reviews: a cross-sectional, descriptive analysis. *BMC Medical Research Methodology* 2011; 11: 160.
2. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JPT. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Statistics in Medicine* 2015; 34(6): 984-98.
3. Rhodes KR, Turner RM, Higgins JPT. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. *Journal of Clinical Epidemiology* 2015; 68(1): 52-60.

4. Rhodes KM, Turner RM, White IR, Jackson D, Spiegelhalter DJ, Higgins JPT. Implementing informative priors for heterogeneity in meta-analysis using meta-regression and pseudo data. *Statistics in Medicine* 2016; 35(29): 5495-511.

METHODOLOGY

Predicting the extent of heterogeneity in meta-analysis, using empirical data from the *Cochrane Database of Systematic Reviews*

Rebecca M Turner,^{1*} Jonathan Davey,¹ Mike J Clarke,² Simon G Thompson³ and Julian PT Higgins¹

¹MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK, ²All-Ireland Hub for Trials Methodology Research, Centre for Public Health, Queen's University Belfast, Northern Ireland and ³Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

*Corresponding author. MRC Biostatistics Unit, Institute of Public Health, Robinson Way, Cambridge CB2 0SR, UK.
E-mail: rebecca.turner@mrc-bsu.cam.ac.uk

Accepted 22 February 2012

Background Many meta-analyses contain only a small number of studies, which makes it difficult to estimate the extent of between-study heterogeneity. Bayesian meta-analysis allows incorporation of external evidence on heterogeneity, and offers advantages over conventional random-effects meta-analysis. To assist in this, we provide empirical evidence on the likely extent of heterogeneity in particular areas of health care.

Methods Our analyses included 14 886 meta-analyses from the *Cochrane Database of Systematic Reviews*. We classified each meta-analysis according to the type of outcome, type of intervention comparison and medical specialty. By modelling the study data from all meta-analyses simultaneously, using the log odds ratio scale, we investigated the impact of meta-analysis characteristics on the underlying between-study heterogeneity variance. Predictive distributions were obtained for the heterogeneity expected in future meta-analyses.

Results Between-study heterogeneity variances for meta-analyses in which the outcome was all-cause mortality were found to be on average 17% (95% CI 10–26) of variances for other outcomes. In meta-analyses comparing two active pharmacological interventions, heterogeneity was on average 75% (95% CI 58–95) of variances for non-pharmacological interventions. Meta-analysis size was found to have only a small effect on heterogeneity. Predictive distributions are presented for nine different settings, defined by type of outcome and type of intervention comparison. For example, for a planned meta-analysis comparing a pharmacological intervention against placebo or control with a subjectively measured outcome, the predictive distribution for heterogeneity is a log-normal ($-2.13, 1.58^2$) distribution, which has a median value of 0.12. In an example of meta-analysis of six studies, incorporating external evidence led to a smaller heterogeneity estimate and a narrower confidence interval for the combined intervention effect.

Conclusions Meta-analysis characteristics were strongly associated with the degree of between-study heterogeneity, and predictive distributions for heterogeneity differed substantially across settings. The informative priors provided will be very beneficial in future meta-analyses including few studies.

Keywords Meta-analysis, heterogeneity, intervention studies, Bayesian analysis

Background

Systematic reviews of randomized trials provide the best evidence on the effectiveness of health-care interventions. Within systematic reviews, results from multiple studies are often combined statistically in a meta-analysis. Differences among the results combined in a meta-analysis arise through genuine differences in the study designs, through differences in the conduct of the research and deviation from the planned designs (biases) and through random variation. In the presence of heterogeneity, it is often considered appropriate to perform a random-effects meta-analysis, in which both the underlying average intervention effect and the between-study heterogeneity are estimated.^{1,2} Many meta-analyses contain only a small number of studies, and this makes it difficult to estimate the between-study variance. A conventional random-effects meta-analysis does not acknowledge the (often substantial) uncertainty in the estimate of the between-study variance.³ A Bayesian meta-analysis offers the benefits of allowing appropriately for this uncertainty, offering a flexible framework for more complex meta-analyses and facilitating prediction of effects in future studies.⁴⁻⁷ Ideally, a Bayesian meta-analysis should be informed by a realistic prior distribution for the between-study variance, based on external evidence.⁸

In principle, meta-analysts could gather evidence on the extent of heterogeneity observed in previous meta-analyses in similar settings, and construct an informative prior distribution for the degree of heterogeneity in their own meta-analysis. However, this is unrealistic in practice. It would therefore be useful if informative prior distributions relevant to a variety of settings were constructed in advance and made available for all to use.

By modelling the data from a large collection of meta-analyses, we have estimated the influence of meta-analysis characteristics on between-study heterogeneity and have obtained predictive distributions for the degree of heterogeneity expected in particular settings. The distributions presented can be used directly in new meta-analyses as ‘off-the-shelf’ prior distributions.

Methods

The contents of the *CDSR* (Issue 1, 2008) were provided to us by the Nordic Cochrane Centre for use in this

research. Many Cochrane reviews include multiple meta-analyses, which correspond to comparisons of different pairs of interventions or the examination of different outcomes within the same overall research topic. For example, a review evaluating antidepressants could report separate meta-analyses comparing each of several antidepressants against placebo, with respect to depression symptoms and adverse effects. In our analyses, we included all meta-analyses of binary outcomes, which reported data from two or more studies. In some cases, review authors had entered data for a set of studies but had chosen not to combine results numerically in a meta-analysis. We included these ‘potential meta-analyses’ as meta-analyses, to maximize the amount of information available, and because the degree of between-study heterogeneity may have influenced the decision not to perform a meta-analysis.

Our focus was on overall heterogeneity in each meta-analysis, and therefore study data were pooled across subgroups, where these had been defined by review authors. For example, subgroups might be defined by geographical location, or by dose of treatment. In some Cochrane reviews, the ‘subgroups’ defined within a meta-analysis were not mutually exclusive, and the same data from a study were included in more than one ‘subgroup’. We therefore checked for duplications by matching study identifiers, and extracted data for only the first occurrence of each study in each meta-analysis.

Classification process

For each meta-analysis in each systematic review, we classified the type of outcome, the types of intervention compared and the medical specialty to which the research question related. The details of this initial stage of work are described elsewhere.⁹ The outcomes, interventions and medical specialties were assigned to fairly narrow categories (see [Table 1](#) footnote), which we grouped together later in our analyses. We based outcome categories on those used by Wood¹⁰ and those proposed by the Foundation for Health Services Research.¹¹ To classify interventions, we used categories based on the Health Research Classification System developed by the UK Clinical Research Collaboration (UKCRC).¹² For medical specialties, we used a taxonomy from the UK National Institute for Health and Clinical Excellence (NICE).¹³ Our initial sets of categories were modified after testing the

Table 1 Distribution of outcome types, intervention comparison types and medical specialty types among the 14 886 meta-analyses in the data set

	Number (%) of meta-analyses
Outcome types^a	
All-cause mortality	1132 (8)
Semi-objective outcomes ^b	4586 (31)
Subjective outcomes ^c	9106 (61)
Intervention comparison types	
Pharmacological vs placebo/control	5599 (38)
Pharmacological vs pharmacological	4118 (28)
Non-pharmacological ^d vs placebo/control	2412 (16)
Non-pharmacological ^d vs non-pharmacological ^d	2442 (16)
Non-pharmacological ^d vs pharmacological	315 (2)
Medical specialty	
Cancer	689 (5)
Cardiovascular	1192 (8)
Central nervous system/musculoskeletal	1210 (8)
Digestive system	1464 (10)
Infectious diseases	780 (5)
Mental health and behavioural conditions	1977 (13)
Obstetrics and gynaecology	3905 (26)
Pathological conditions	414 (3)
Respiratory diseases	1310 (9)
Urogenital	932 (6)
Other specialties	1013 (7)

^aSixty-two meta-analyses were excluded where the outcome did not fit into any of our pre-defined categories and was classified as 'Other'.

^bSemi-objective outcomes include cause-specific mortality, major morbidity event, composite mortality/morbidity, obstetric outcomes, internal structure, external structure, surgical device success/failure, withdrawals/drop-outs, resource use, hospital stay/process measures.

^cSubjective outcomes include pain, mental health outcomes, dichotomous biological markers, quality of life/functioning, consumption, satisfaction with care, general physical health, adverse events, infection/new disease, continuation/termination of condition being treated, composite endpoint (including at most one mortality/morbidity endpoint).

^dNon-pharmacological interventions include interventions classified as medical devices, surgical, complex, resources and infrastructure, behavioural, psychological, physical, complementary, educational, radiotherapy, vaccines, cellular and gene and screening.

classification process in a pilot study that included 50 systematic reviews.

Wherever possible, outcomes and interventions were classified on the basis of short text descriptions

provided by the review authors, together with the title of the systematic review. Where additional information was required, we consulted descriptions of the outcomes, interventions and participants in the five studies receiving greatest weight in the meta-analysis. Medical specialties were classified usually on the basis of the title of the systematic review, or on the review abstract if clarification was needed.

Statistical analysis

We used hierarchical models to analyse the study data from all included meta-analyses simultaneously, while investigating the effects of meta-analysis characteristics on the level of between-study heterogeneity. Within each meta-analysis, a random-effects model with binomial within-study likelihoods was fitted to the binary outcome data from each study on the log odds ratio (OR) scale. Across meta-analyses, a hierarchical regression model was fitted to the log-transformed values of underlying between-study heterogeneity variance τ^2 , assuming a normal distribution for the residual variation. As covariates in the regression model, we included indicators of outcome type, intervention comparison type and medical specialty, and number of studies in the meta-analysis (log-transformed, as a continuous covariate). Heterogeneity was assumed to vary across meta-analyses within pair-wise comparisons with separate variances for different outcome types. Heterogeneity was also assumed to vary across pair-wise comparisons, with separate variances for different intervention comparison types. The algebraic form of the models is provided in the [Supplementary Appendix S1](#).

All models were fitted within a Bayesian framework, and estimation was achieved using the WinBUGS software.¹⁴ Results were based on 50 000 iterations following a burn-in of 5000 iterations, which was sufficient to achieve convergence. Model selection was performed using the deviance information criterion (DIC).¹⁵ We declared $N(0,10)$ priors for all regression coefficients, and declared $Uniform(0,2)$ priors for the standard deviations of the random effects representing variation in heterogeneity across outcomes within comparisons and across pair-wise comparisons.

On the basis of the findings from the above analyses, we chose to focus on a small set of three outcome types and three intervention comparison types. For each pair-wise combination among these, we obtained a predictive distribution for the between-study heterogeneity τ_{new}^2 expected in a future meta-analysis in this setting. A log-normal distribution was fitted to each predictive distribution, using the posterior mean and standard deviation for $\log(\tau_{new}^2)$. This process provides parametric distributions approximating the predictive distributions obtained from the full Bayesian model, so they can be easily summarized and reported for use in future meta-analyses.

Table 2 Structure of data set: number of pair-wise comparisons per review, meta-analyses per comparison, studies per meta-analysis and size of study

	N	Min	25% Percentile	Median	75% Percentile	Max
Number of comparisons per review	1991 reviews	1	1	1	2	20
Number of meta-analyses per comparison	3884 comparisons	1	1	2	5	43
Number of studies per meta-analysis	14 886 meta-analyses	2	2	3	6	294
Sample size	77 237 studies	2	50	102	243	1 242 071

Results

Characteristics of data set

The data set includes 14 886 meta-analyses from 1991 Cochrane reviews, containing data from 77 237 individual studies in total. Table 2 shows the structure of the data set. The number of meta-analyses per pair-wise comparison ranged from 1 to 43 with a median of 2. The median number of studies included in a meta-analysis was 3 with range 2–294 (a meta-analysis had to contain at least two studies to be eligible). The median number of participants in the studies in the meta-analyses varied substantially, from studies of only two individuals to very large studies containing over a million individuals. In 8595 (57%) of the meta-analyses, the method of moments estimate τ^2 for between-study heterogeneity was set to 0. Figure 1 shows the distribution of the non-zero estimates. We note that zero estimates τ^2 are often obtained when true between-study heterogeneity τ^2 is small but positive.

Table 1 presents the frequencies of different outcome types, intervention comparison types and medical specialties among the meta-analyses included in this data set. We regarded all-cause mortality as the most objectively assessed outcome, and this was used in 8% of the meta-analyses. All other outcome categories were grouped together as ‘semi-objective outcomes’ or ‘subjective outcomes’; the details are given in Table 1. Each meta-analysis compares a pair of interventions, which were classified separately according to a list of 17 categories (pharmacological, psychological, surgical etc.).⁹ In this article, we group these into broader categories: pharmacological, non-pharmacological and placebo/control. Meta-analyses comparing pharmacological interventions against placebo or control were the most frequent (38%), whereas meta-analyses comparing pharmacological against pharmacological interventions (i.e. head-to-head comparisons) formed the second largest group (28%). The frequency of different medical specialties is shown in Table 1. Obstetrics and gynaecology was the most frequently occurring category (26% of meta-analyses).

Comparing heterogeneity across meta-analysis types

Ratios of heterogeneity variances τ^2 between different types of meta-analysis are presented in Table 3.

Meta-analyses in which the outcome was all-cause mortality displayed substantially lower between-study heterogeneity than other meta-analyses; the ratio of variances was estimated as 0.17 (95% CI 0.10–0.26). Heterogeneity was substantially lower in meta-analyses assessing all-cause mortality compared with those assessing subjective outcomes, and also lower in meta-analyses of semi-objective outcomes than in meta-analyses of subjective outcomes.

In terms of intervention types, heterogeneity was on average lowest in pharmacological vs pharmacological meta-analyses, with evidence of a difference compared with meta-analyses involving non-pharmacological interventions. Heterogeneity also tended to be lower in meta-analyses comparing pharmacological vs placebo/control than in non-pharmacological meta-analyses, but the confidence interval for the ratio included the null value 1.

Overall, there was no evidence of differences in between-study heterogeneity among medical areas (inclusion of medical specialty indicators led to worse model fit, as assessed by the DIC). Meta-analysis size was found to have a small effect on between-study heterogeneity; the τ^2 ratio corresponding to a doubling in the number of studies was estimated as 1.11 (95% CI 1.03–1.18).

To explore sensitivity to our choices in constructing the data set, we performed repeats of the primary analysis reported in Table 3, within three different versions of the data set: firstly, we excluded 529 ‘potential meta-analyses’ which had chosen not to pool results; second, we used data from the first subgroup only, for 5186 meta-analyses including subgroups; third, we excluded 5081 meta-analyses including only two studies. In each analysis, the central estimates for the ratios comparing different types of meta-analyses remained similar to those reported, whereas the 95% CIs widened to reflect the smaller sample size.

Predictive distributions for heterogeneity in future meta-analyses

We first reported a predictive distribution for between-study heterogeneity in a future meta-analysis in a general setting. This was obtained from a hierarchical model fitted to all meta-analyses in the data set, including no meta-analysis characteristics as covariates. The fitted distribution for τ_{new}^2 was

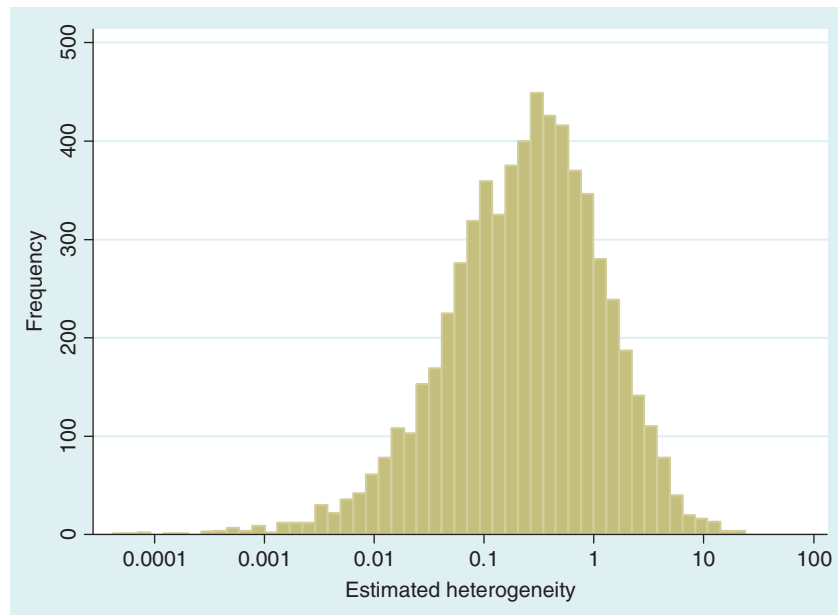


Figure 1 Distribution of non-zero estimates for between-study heterogeneity variance (τ^2), plotted on log scale

Table 3 Ratios of variances representing comparisons of between-trial heterogeneity τ^2 among different types of meta-analysis, according to intervention comparison, outcome, medical specialty and size (number of trials)

Comparisons based on meta-analysis characteristics	Ratio of τ^2 (95% CI)
Outcome types^a	
All-cause mortality / All other outcomes	0.17 (0.10–0.26)
All-cause mortality / Subjective ^b outcomes	0.14 (0.07–0.22)
Semi-objective ^b outcomes / Subjective ^b outcomes	0.45 (0.37–0.55)
Intervention comparison types^c	
Pharmacological vs placebo/control / Non-pharmacological ^b (any)	0.94 (0.76–1.13)
Pharmacological vs pharmacological / Non-pharmacological ^b (any)	0.75 (0.58–0.95)
Medical specialty types^d	
Cancer / Obstetrics and gynaecology	0.95 (0.65–1.35)
Cardiovascular / Obstetrics and gynaecology	0.55 (0.40–0.75)
Central nervous system or musculoskeletal disorders / Obstetrics and gynaecology	0.85 (0.60–1.16)
Digestive system / Obstetrics and gynaecology	1.23 (0.93–1.58)
Infectious diseases / Obstetrics and gynaecology	1.46 (1.05–1.96)
Mental health and behavioural conditions / Obstetrics and gynaecology	1.03 (0.80–1.31)
Pathological conditions / Obstetrics and gynaecology	1.56 (1.09–2.33)
Respiratory diseases / Obstetrics and gynaecology	0.70 (0.51–0.98)
Urogenital / Obstetrics and gynaecology	1.81 (1.28–2.59)
Other specialties / Obstetrics and gynaecology	1.14 (0.86–1.51)
Number of studies in meta-analysis: ratio corresponding to 5-study increase ^e	1.02 (1.00–1.04)

^aAnalysis adjusted for intervention comparison type and medical specialty type.

^bSubjective and semi-objective outcomes and non-pharmacological interventions defined in Table 2.

^cAnalysis adjusted for outcome type and medical specialty type.

^dAnalysis adjusted for intervention comparison type and outcome type.

^eAnalysis adjusted for intervention comparison type, outcome type and medical specialty type.

Table 4 Predictive distributions^a obtained for the between-study heterogeneity τ_{new}^2 in a future meta-analysis, across nine different settings

Outcome type	Intervention comparison type		
	Pharmacological vs Placebo/Control	Pharmacological vs Pharmacological	Non-pharmacological ^b (any)
All-cause mortality	Log-normal (−4.06,1.45 ²): median = 0.017; 95% range = (0.001–0.30)	Log-normal (−4.27,1.48 ²): median = 0.014; 95% range = (0.0008–0.25)	Log-normal (−3.93,1.51 ²): median = 0.020; 95% range = (0.001–0.38)
Semi-objective ^b	Log-normal (−3.02,1.85 ²): median = 0.049; 95% range = (0.001–1.83)	Log-normal (−3.23,1.88 ²): median = 0.040; 95% range = (0.001–1.58)	Log-normal (−2.89,1.91 ²): median = 0.056; 95% range = (0.001–2.35)
Subjective ^b	Log-normal (−2.13,1.58 ²): median = 0.12; 95% range = (0.005–2.63)	Log-normal (−2.34,1.62 ²): median = 0.096; 95% range = (0.004–2.31)	Log-normal (−2.01,1.64 ²): median = 0.13; 95% range = (0.005–3.33)

^aFitted distributions reported as log-normal(μ, σ^2), where μ and σ are the mean and SD on the log scale. We also report medians and 2.5% and 97.5% quantiles on the untransformed scale.

^bSubjective and semi-objective outcomes and non-pharmacological interventions defined in Table 2.

estimated as log-normal (−2.56,1.74²), which has median 0.08 and 95% range 0.003–2.34 on the untransformed τ^2 scale.

Table 4 summarizes a set of log-normal distributions fitted to the predictive distributions for the between-study heterogeneity expected in a future meta-analysis in each of nine different settings, defined by outcome type and intervention comparison type. The differences among these fitted distributions reflect the findings reported in Table 3. There are substantial differences across the three outcome types; the fitted distributions for meta-analyses of an all-cause mortality outcome have much lower medians and 97.5% quantiles, whereas the predictive distributions for a subjective outcome have the highest medians and 97.5% quantiles. Differences among the three types of intervention comparison considered are smaller, but show a consistent pattern within each outcome type: the lowest levels of heterogeneity are expected in meta-analyses of pharmacological vs pharmacological comparisons and the highest levels in comparisons that assess a non-pharmacological intervention.

Figure 2 illustrates the predictive distributions for between-study heterogeneity in two very different settings: a pharmacological vs placebo/control meta-analysis with an all-cause mortality outcome; and a non-pharmacological meta-analysis with a subjective outcome. The empirical distribution obtained from the full Bayesian model is plotted as a histogram in each case, whereas the black line represents the fitted log-normal distribution (as summarized in Table 4). For a pharmacological vs placebo/control meta-analysis measuring all-cause mortality, the predictive distribution for τ_{new}^2 gives little support to values above 0.2, whereas the predictive distribution for a non-pharmacological meta-analysis measuring a subjective outcome gives moderate support to

heterogeneity values up to 1. To illustrate the implications for variability in ORs, we calculate expected 95% ranges for underlying ORs in pharmacological vs placebo/control meta-analyses assessing different outcome types. Based on the median-predicted values for τ_{new}^2 (Table 4), we expect ORs with 95% ranges of 0.77–1.29 for all-cause mortality, 0.65–1.54 for semi-objective outcomes and 0.51–1.97 for subjective outcomes, assuming a central value of 1.

Application to an example meta-analysis

To illustrate the use of an informative prior for heterogeneity, we re-analysed the data from a published meta-analysis including six studies.¹⁶ The meta-analysis evaluates the effectiveness of granulocyte (white blood cell) transfusions for treating patients with neutropenia or neutrophil dysfunction, who are at high risk of serious infections and death. In a conventional random-effects meta-analysis of these data (Figure 3), the heterogeneity estimate was high ($\hat{\tau}^2 = 1.27$, $I^2 = 65\%$) but imprecisely estimated (Table 5). Since few studies were available, the $\hat{\tau}^2$ estimate was strongly influenced by the extreme result from the Higby study, and would reduce to 0.13 if this study were excluded.

Table 5 presents results from a Bayesian meta-analysis using a vague Uniform (0,5) prior for τ . Estimation was achieved within the WinBUGS software,¹⁴ and results were based on 50 000 iterations following a burn-in of 5000 iterations. This analysis produced an extremely wide interval for τ^2 , and a correspondingly widened interval for the combined OR, which reflects the uncertainty in τ^2 . When so few studies are included, the results are known to be very sensitive to choice of vague prior for τ^2 ,¹⁷ and little confidence would be placed in these results.

The granulocyte transfusions meta-analysis evaluated a non-pharmacological intervention with respect

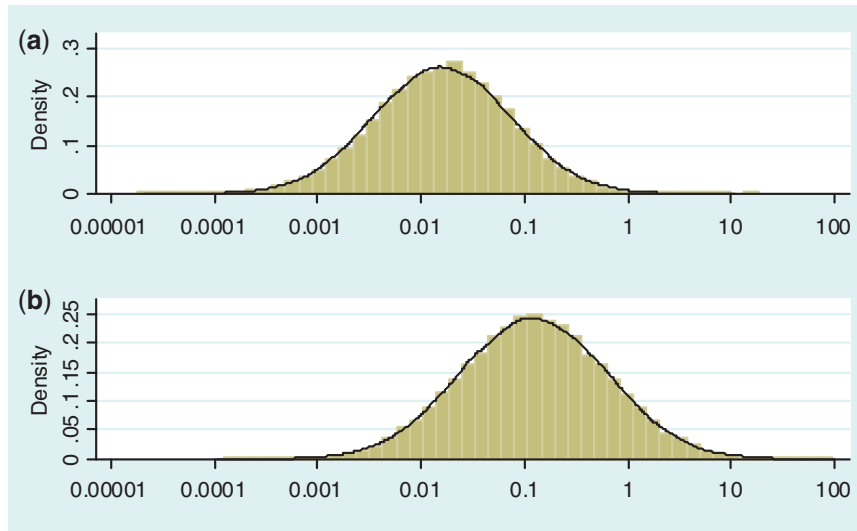


Figure 2 Predictive distributions for heterogeneity variance (plotted on log scale) in: (a) pharmacological vs placebo/control meta-analysis measuring all-cause mortality; (b) non-pharmacological meta-analysis measuring a subjective outcome

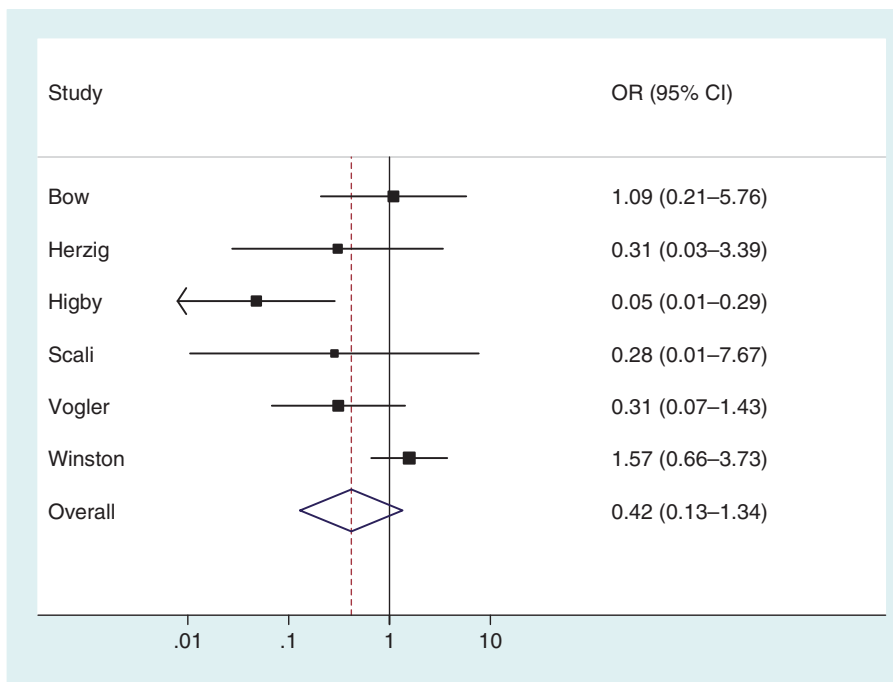


Figure 3 Conventional random-effects meta-analysis combining results from six studies on the effectiveness of granulocyte (white blood cell) transfusions for prevention of mortality in patients with neutropenia or neutrophil dysfunction¹⁶

to all-cause mortality, so we used a log-normal $(-3.93, 1.51^2)$ distribution as an informative prior distribution for τ^2 (Table 4). The simple code for fitting the model is available in the [Supplementary Appendix S1](#). When using an informative prior, the central estimate for heterogeneity reduced to 0.18 (95% CI 0.003–1.70), and the interval for the combined OR narrowed substantially (Table 5). Since the informative prior represents our beliefs about likely values

of heterogeneity in this meta-analysis, we would consider these results appropriate as a primary analysis of the data.

As a contrasting example, we have also re-analysed the data from a published meta-analysis of six studies in which the conventional heterogeneity estimate was low ($\hat{\tau}^2 = 0.02$, $I^2 = 6\%$), but again imprecisely estimated (Table 5). This meta-analysis evaluated the effectiveness of the antidepressant nortriptyline

Table 5 Application to example meta-analyses: comparison of results obtained from conventional and Bayesian approaches to random-effects meta-analysis

	Combined OR estimate (95% CI)	Heterogeneity variance estimate τ^2 (95% CI)
Granulocyte (white blood cell) transfusions vs no transfusions. Outcome: all-cause mortality		
Conventional random-effects meta-analysis (DerSimonian and Laird estimation)	0.42 (0.13–1.34)	1.25 (0.04–8.50) ^a
Bayesian random-effects meta-analysis with Uniform(0,5) prior for τ	0.33 (0.03–1.96)	2.74 (0.34–18.1)
Bayesian random-effects meta-analysis with log-normal ($-3.93, 1.51^2$) prior for τ^2	0.48 (0.18–1.01)	0.18 (0.003–1.70)
Nortriptyline vs placebo. Outcome: long-term abstinence (6–12 months) from smoking		
Conventional random-effects meta-analysis (DerSimonian and Laird estimation)	2.26 (1.52–3.37)	0.02 (0–1.86) ^a
Bayesian random-effects meta-analysis with Uniform (0,5) prior for τ	2.40 (1.28–4.77)	0.13 (0.0003–2.50)
Bayesian random-effects meta-analysis with log-normal ($-2.13, 1.58^2$) prior for τ^2	2.39 (1.50–3.91)	0.07 (0.004–0.64)

^aConfidence interval for τ^2 calculated using Q-profile method.¹⁹

for smoking cessation.¹⁸ When performing a Bayesian meta-analysis using an informative prior for τ^2 , the central estimate of τ^2 increased slightly to 0.07 whereas its 95% CI narrowed. This Bayesian meta-analysis allows appropriately for the imprecision in τ^2 and produces a wider interval for the combined OR in comparison with a conventional random-effects meta-analysis.

Discussion

Many meta-analyses synthesize the evidence from only a small number of studies, which makes estimation of the between-study variance difficult. A Bayesian approach to estimation is particularly beneficial in small meta-analyses, since it allows incorporation of external evidence on the between-study variance. In this article, we have analysed a large database of meta-analyses in order to describe the predictors of between-study heterogeneity and construct informative prior distributions for the heterogeneity variance. We have shown how these priors can be used in a future meta-analysis, and provided an example where precision is improved by doing so.

Informative prior distributions for between-study heterogeneity have been proposed previously. Smith *et al.*⁴ derived an informative prior distribution for heterogeneity in a binary data meta-analysis by considering the degree of spread of ORs which could reasonably be expected. Higgins and Whitehead⁸ constructed a prior distribution for a meta-analysis in gastroenterology, by fitting an inverse gamma distribution to the heterogeneity parameters of 18 meta-analyses of similar study types. Pullenayegum²⁰ recently analysed 314 meta-analyses from the *CDSR*

and developed a joint prior for heterogeneity and the pooled log OR, allowing the prior for heterogeneity to depend on the magnitude of the intervention effect. In our models, we allowed heterogeneity to depend only on known meta-analysis characteristics, in order that the priors can be fully specified in advance of the analysis and implementation is straightforward. The size and breadth of the full *CDSR* data set have enabled us to identify important predictors of heterogeneity and construct a number of priors for specific meta-analysis types.

A limitation of our work is that the data set only includes data entered numerically by the systematic review authors. Meta-analyses reported only in the text of a systematic review may tend to exhibit higher between-study heterogeneity, so we expect our analyses to under-estimate the true levels of heterogeneity. Second, the data set includes only meta-analyses from Cochrane reviews, which are not necessarily representative of meta-analyses in general. Another limitation is that the classifications of meta-analysis characteristics were carried out by only one person, owing to the very large amount of work involved. In our current work, we have analysed meta-analyses of binary outcomes only, and the informative priors cannot be applied directly to other outcome types.

In our analyses, we have modelled total between-study heterogeneity, which is likely to comprise a mixture of variation caused by true diversity among the protocols for the original studies, variation caused by biases and unexplained variation. Assuming that a conventional random-effects model will be used in many future meta-analyses, it is appropriate to focus on total between-study heterogeneity in our predictive findings. However, it would be preferable to separate

variation attributable to biases from other sources of between-study variation. In later versions of the *CDSR*, this will become possible once the recently introduced Cochrane risk-of-bias tool²¹ has been implemented in a large number of systematic reviews. Our existing hierarchical model for the data from all available meta-analyses could be extended to incorporate the bias model proposed by Welton *et al.*²² This would allow us to adjust for the bias attributable to a potential source (e.g. inadequate allocation concealment) in all studies judged to be at high risk. In principle, the model could be extended further to adjust for multiple sources of bias simultaneously. Results from this analysis could provide useful information about the degree to which one would expect between-study heterogeneity to reduce, on average, if meta-analysts chose to adjust for known sources of bias, for example, by using empirical evidence or elicited opinion on biases.^{22,23}

In summary, between-study heterogeneity was found to be strongly associated with the type of outcome measured in the meta-analysis, with meta-analyses of all-cause mortality or semi-objective outcomes exhibiting substantially lower heterogeneity than meta-analyses of subjective outcomes. Heterogeneity may also be associated with intervention comparison type, to a lesser extent. Informative priors for heterogeneity would be beneficial in meta-analyses including few studies, and these have been made available in this report.

In view of the important influences on heterogeneity observed in the *CDSR* data set, use of an informative prior for heterogeneity in future meta-analyses would be entirely justifiable.

Supplementary Data

Supplementary Data are available at *IJE* online.

Funding

Medical Research Council Population Health Sciences Research Network (grant number U.1052.00.011.00003.01).

Acknowledgements

We are grateful to the Nordic Cochrane Centre (particularly Rasmus Moustgaard and Monica Kjeldstrøm) and the Cochrane Collaboration Steering Group for providing us with access to the *Cochrane Database of Systematic Reviews*. We thank David Spiegelhalter, Jonathan Sterne, Tony Ades, Nicky Welton and Sofia Dias for discussions during the development of the project.

Conflict of interests: None declared.

KEY MESSAGES

- Many meta-analyses contain only a small number of studies, which makes it difficult to estimate the extent of between-study heterogeneity.
- By analysing a large database of meta-analyses, we have identified important predictors of heterogeneity.
- Prior distributions for heterogeneity have been constructed for use in specific topic areas. These would be very beneficial in future meta-analyses including few studies.

References

- ¹ DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials* 1986;**7**:177–88.
- ² Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J Royal Stat Soc A* 2009;**172**:137–59.
- ³ Jackson D, Bowden J, Baker R. How does the DerSimonian and Laird procedure for random effects meta-analysis compare with its more efficient but harder to compute counterparts? *J Stat Plan Infer* 2010;**140**:961–70.
- ⁴ Smith TC, Spiegelhalter DJ, Thomas A. Bayesian approaches to random-effects meta-analysis: a comparative study. *Stat Med* 1995;**14**:2685–99.
- ⁵ Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res* 2001;**10**:277–303.
- ⁶ Higgins JPT, Spiegelhalter DJ. Being sceptical about meta-analyses: a Bayesian perspective on magnesium trials in myocardial infarction. *Int J Epidemiol* 2002;**31**:96–104.
- ⁷ Ades AE, Lu G, Higgins JPT. The interpretation of random-effects meta-analysis in decision models. *Med Decis Making* 2005;**25**:646–54.
- ⁸ Higgins JPT, Whitehead A. Borrowing strength from external trials in a meta-analysis. *Stat Med* 1996;**15**:2733–49.
- ⁹ Davey J, Turner RM, Clarke MJ, Higgins JPT. Characteristics of meta-analyses and their component studies in the *Cochrane Database of Systematic Reviews*: a cross-sectional, descriptive analysis. *BMC Med Res Methodol* 2011;**11**:160.
- ¹⁰ Wood L. *The Epidemiology of Bias in Randomized (clinical) Controlled Trials: a Meta-epidemiological Study*. PhD thesis. University of Bristol, 2006.

- ¹¹ Foundation for Health Services Research. *Health Outcomes Research: A Primer*. <http://www.academyhealth.org/files/publications/healthoutcomes.pdf> (1 March 2011, date last accessed).
- ¹² UK Clinical Research Collaboration. *Health Research Classification System*. http://www.hrcsonline.net/pages/hrcs_download (1 March 2011, date last accessed).
- ¹³ National Institute for Health and Clinical Excellence. *NICE Taxonomy* (subject encoding scheme). http://www.nice.org.uk/aboutnice/nicewebsitedevelopment/standards/metadata/niceencodingschemes/nice_encoding_schemes.jsp (1 August 2009, date last accessed).
- ¹⁴ Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS—a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput* 2000;**10**:325–37.
- ¹⁵ Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian measures of model complexity and fit (with discussion). *J Royal Stat Soc B* 2002;**64**:583–640.
- ¹⁶ Stanworth S, Massey E, Hyde C *et al*. Granulocyte transfusions for treating infections in patients with neutropenia or neutrophil dysfunction. *Cochrane Database Syst Rev* 2010, Issue 8; Art. No.: CD005339.
- ¹⁷ Lambert PC, Sutton AJ, Burton PR, Abrams KR, Jones DR. How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS. *Stat Med* 2005;**24**:2401–28.
- ¹⁸ Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2011, Issue 8; Art. No.: CD000031.
- ¹⁹ Viechtbauer W. Confidence intervals for the amount of heterogeneity in meta-analysis. *Stat Med* 2007;**26**: 37–52.
- ²⁰ Pullenayegum E. An informed reference prior for between-study heterogeneity in meta-analyses of binary outcomes. *Stat Med* 2011;**30**:3082–94.
- ²¹ Higgins JPT, Altman DG. Assessing risk of bias in included studies. In: Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: John Wiley & Sons, 2008, pp. 187–241.
- ²² Welton NJ, Ades AE, Carlin JB, Altman DG, Sterne JAC. Models for potentially biased evidence in meta-analysis using empirically based priors. *J Royal Stat Soc A* 2009; **172**:119–36.
- ²³ Turner RM, Spiegelhalter DJ, Smith GCS, Thompson SG. Bias modelling in evidence synthesis. *J Royal Stat Soc A* 2009;**172**:21–47.